II.D.4.

One of the principal effects of pH adjustment is to alter the rate of drug delivery to the target receptors in the body. The rate of drug delivery is well known to affect a wide range of pharmacological effects for numerous drug products. For example, a slow rate of absorption is the critical reason that nicotine patches do not produce mood-altering effects.[1067] These effects occur only when nicotine is absorbed quickly into the body.

FDA conducted tests to assess the speed of nicotine transfer across the membranes using smokeless tobacco with different pH levels. The results showed that, consistent with scientific theory, pH levels affected nicotine transfer: nicotine from the high-pH product was transferred across membranes more quickly than was nicotine from the low-pH product. In fact, in the first 2 minutes, the amount of nicotine released from a typical size pinch of Copenhagen, a product with a high pH, was 12 times higher than the amount of nicotine released from a Skoal Bandit pouch, a product with a low pH.[1068]

For these reasons, FDA finds that there is an adequate scientific basis to conclude that in vitro pH values predict changes in nicotine delivery.

3. One smokeless tobacco industry comment presents a study performed by Andersson,[1069] which it claims refutes FDA's reliance on in vitro pH data. The comment states that the Andersson study demonstrated higher levels of nicotine in users of lower pH chewing tobacco than in users of higher pH moist snuff. According to the comment,

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[1067] Benowitz NL, Pharmacodynamics of nicotine: implications for rational treatment of nicotine addiction, *British Journal of Addiction* 1991;86:495-499, at 496. *See* AR (Vol. 71 Ref. 52).

[1068] *See* Ciolino L, *Moist Snuff Nicotine Release Studies* (Sep. 28, 1994), at 2. *See* AR (Vol. 30 Ref. 500-2).

[1069] Andersson G, Bjornberg G, Curvall M, Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: a comparative study, *J Oral Pathol Med* 1994:161-167. *See* AR (Vol. 526 Ref. 95, vol. VII).

Andersson's data demonstrate that the smokeless tobacco product with the highest pH (8.5 to 8.6) had the poorest buccal absorption of nicotine. The comment argues that these data support the contention that smokeless tobacco pH is irrelevant to nicotine absorption in the smokeless tobacco user.

FDA disagrees with this comment. In fact, the Andersson study found that the degree of nicotine extraction was "significantly higher" among users of loose moist snuff than among users of moist snuff in pouches.[1070] This finding is consistent with FDA's analysis, because the loose moist snuff had a higher pH than the moist snuff in pouches.[1071]

Moreover, the comment mischaracterizes the Andersson findings in other ways as well. First, the study did not compare absorption characteristics on a gram-for-gram basis across products differing in pH. For example, the smokeless tobacco product with the highest absorption, a type of chewing tobacco, had over twice as much nicotine in it as any of the moist snuff products used in this study and subjects in the study used varying amounts of smokeless tobacco. Thus, nicotine absorption in the study could have been affected by the uncontrolled variation in the amount of nicotine consumed, confounding the effects of pH on nicotine absorption.

Second, the study measured nicotine blood levels at only one time point, which is inadequate to determine nicotine absorption (rate or extent). Third, the authors did not claim that the study demonstrated anything about the effects of pH on absorption.

[1070] *Id.* at 164.

[1071] *Id.*

Thus, the Andersson study provides no support for the argument that in vitro data are inadequate to describe the amount of nicotine available for absorption.

4. The comments from the smokeless tobacco industry state that a variety of biological and behavioral factors are stronger determinants of nicotine absorption than the pH of the product. The comments cite such factors as the length of time the smokeless tobacco is left in the mouth, the extent to which the smokeless tobacco is "worked" by the user, the rate and volume of expectorate, and the frequency and amount of swallowing, as well as salivary pH.

FDA agrees that other factors can influence nicotine absorption besides pH levels. Moreover, some of these additional factors are within the control of the manufacturer, including the use of pouches for some products; additives, such as humectants; the cut of the tobacco; and the use of various binding agents. Nonetheless, the role of these other factors appears to be less significant. The UST report entitled "Pharmacokinetics of Nicotine and its Major Metabolites in Naive and Habituated Snuff Takers," for instance, concluded, that after using identical portions of snuff there "appears to be no differences" in plasma nicotine levels between inexperienced and experienced smokeless tobacco users.[1072] One would expect many of the factors cited by the comment, including rate and volume of expectorating, and frequency and amount of swallowing, to differ between inexperienced and experienced users, but these differences apparently did *not* affect amount of nicotine absorption in the two groups.

[1072] U.S. Tobacco, *Pharmacokinetics of Nicotine and its Major Metabolites in Naive and Habituated Snuff Takers*, UST document from *Marsee*, plaintiff's exhibit 3.27 at 13. *See* AR (Vol. 344 Ref. 5436).

Similarly, the final results from a preliminary study cited by the smokeless tobacco industry concluded that "buccal nicotine absorption was *not* affected by saliva discharge rate."[1073] These results are similar to those of a companion study by Nemeth-Coslett *et al.*, which studied the effect of the chewing rate on nicotine absorption from nicotine gum.[1074] In another study by these researchers, pH was varied, producing a strong effect on nicotine absorption from nicotine gum. In this companion study, there was minimal absorption under acidic conditions and significant absorption under alkaline conditions.[1075] Taken together, these studies show that the effects of pH on nicotine absorption are more significant than the effects of oral manipulation.

Moreover, behavioral factors should have a minor impact when comparing the effect of a series of smokeless tobacco on a given user, because the habits of the user should be relatively constant. Therefore, for any individual smokeless tobacco user, a product line with graduated pH levels will produce graduated nicotine deliveries.

In conclusion, although the Agency agrees that biological and behavioral factors can influence absorption of nicotine, the Agency finds that product pH has an established and significant role in controlling the absorption of nicotine.

5. A smokeless tobacco industry comment emphasizes the role of saliva and states that the pH levels of smokeless tobacco do not influence nicotine absorption. The

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[1073] Cohen C, Radzius A, Simmons E, *et al.*, *Time course of buccal nicotine absorption* (NIDA unpublished report, 1994) (emphasis added). *See* AR (Vol. 711 Ref. 15).

[1074] Nemeth-Coslett R, Benowitz NL, Robinson N, *et al.*, Nicotine gum: chew rate, subjective effects and plasma nicotine, *Pharmacology, Biochemistry, & Behavior* 1988;29:747-751. *See* AR (Vol. 711 Ref. 10).

[1075] Henningfield JE, Radzius A, Cooper TM, *et al.*, Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum, *Journal of the American Medical Association* 1990; 264:1560-1564. *See* AR (Vol. 29 Ref. 491-2).

comment argues that FDA data show that the buffering capacity of saliva is greater than that of smokeless tobacco. Thus, according to the comment, when the smokeless tobacco and saliva mix in the mouth, the resultant pH of the mixture is determined by the saliva and not the tobacco.

FDA disagrees with this comment. FDA assessed the buffering capacity of saliva in a report entitled "Relative Buffering Capacity of Saliva and Moist Snuff."[1076] This study tested 1-ml, 2.5-ml, 5-ml, and 10-ml volumes of saliva.[1077] For each brand of smokeless tobacco tested, the product pH was measured and a 1.5g quantity of tobacco, representing a typical pinch, was selected. The effect of saliva volume on the resultant pH of saliva/moist snuff mixtures was then evaluated. Contrary to the comments of the smokeless tobacco manufacturers, the results of this study indicate that the saliva pH was altered by addition of the smokeless tobacco at all saliva volumes tested, demonstrating that product pH will influence the amount of free nicotine available for absorption.

FDA's Artificial Saliva Study, which is cited by the comment, does not conflict with these results. As clearly stated in the FDA memorandum summarizing the study, the Artificial Saliva Study was designed to measure and compare the rate of nicotine release from smokeless tobacco. The study did not measure smokeless tobacco effects on the pH of the artificial saliva.[1078]

[1076] Memorandum from Ciolino L, *Relative Buffering Capacity of Saliva and Moist Snuff.* (Sep. 28, 1994). *See* AR (Vol. 29 Ref. 499).

[1077] *Id.* at 2.

[1078] Memorandum from Ciolino L, *Moist Snuff Nicotine Release Studies* (Sep. 28, 1994), at table IV.B. *See* AR (Vol. 30 Ref. 500-2).

Moreover, there are several reasons why the Artificial Saliva Study cannot be used to answer the question of whether saliva pH or product pH dominates in the absorption process for nicotine from smokeless tobacco. First, the experiments in the Artificial Saliva Study were conducted for all of the products using only 0.5g of smokeless tobacco. This amount (0.5g) was used because this is the net tobacco weight in the Skoal Bandits pouch and because the purpose of this study was to make a controlled comparison among products. As stated in the FDA memo, however, 1.5g of tobacco more closely represents a typical "pinch" for Copenhagen, as well as for Skoal Long Cut Wintergreen and Skoal Original Fine Cut Wintergreen.[1079] Thus, the amount of product used in the experiments is three times lower than in typical use conditions for the latter three products, and certainly no conclusion can be drawn from this study as to whether salivary pH or product pH would dominate under typical use conditions.

Second, the experiments in the Artificial Saliva Study were conducted using 10 ml of saliva. Although there is about 10 ml of saliva in the human mouth, the volume of saliva that contacts the plug of moist snuff when it is initially placed in the mouth and used as directed is much less than 10 ml. When used as directed by the manufacturers, moist snuff is intended to stay in one place in the mouth, limiting mixing with saliva. Its use does not require the active oral manipulation and accompanying salivary saturation of chewing tobacco products. A pinch or a pouch of moist snuff is a self-contained dosing unit that is wedged between the gum and cheek in such a manner that it would be relatively protected from rapid saturation by saliva.

[1079] *Id.* at 1.

Indeed, the industry's own instructions to users are to lodge the product between the cheek and gum to minimize such mixing or float. In direct marketing and advertising campaigns, new users are specifically instructed on how to use moist snuff products to minimize mixing with saliva. For example, in a UST advertisement entitled "Walt Garrison answers your questions about smokeless tobacco," the advertising copy states: "Just take a small pinch between your thumb and forefinger, put it between your cheek and gum, and leave it there. The tobacco will slowly release its great flavor to give you real tobacco satisfaction."[1080] In another UST advertisement, the instructions are consistent: "How do I use Skoal Bandits? Simply take a pouch and place it between your upper lip and gum. Leave it there, but DON'T CHEW IT. The pouch works like a teabag, holding the tobacco in, but letting the flavour out."[1081] These instructions to consumers minimize salivary mixing and oral dissolution of the products. The less saliva contacts the product, the more the product pH controls absorption.

Third, the product pH's of the particular tins of smokeless tobacco used in the Artificial Saliva Study were not determined. Without knowing the product pH levels, the relative effects of saliva and product on the net solution pH after addition of the product cannot be evaluated. When discussing FDA's Artificial Saliva Study, the comment misrepresented pH levels that were measured as part of the Reproducibility Study portion of this work as the product pH levels. The measurements in the Reproducibility Study were made on different lots of smokeless tobacco than were used in the Artificial Saliva Study.

[1080] Ernster VL, Advertising and promotion of smokeless tobacco products, *Monographs/National Cancer Institute* 1989:87-94, at 90. *See* AR (Vol. 65 Ref. 853).

[1081] Advertisement: "Introducing Skoal Bandits, The new way to enjoy tobacco." *See* AR (Vol. 241 Ref. 3260).

The smokeless tobacco manufacturers themselves argue that there is lot-to-lot variability for product pH. Accordingly, the products' pH from the Reproducibility Study were not necessarily the same as the pH of the products tested in the Artificial Saliva Study.

In conclusion, the comment mischaracterized the Agency's laboratory data and drew erroneous conclusions from the data presented. In fact, FDA's analyses shows that the pH of smokeless tobacco affects the pH levels of the saliva in contact with the smokeless tobacco, thereby controlling the level of nicotine absorption.

6. One smokeless tobacco industry comment states that solids, such as tobacco, cannot have a pH value.

Solid materials must mix with a liquid before the product's pH is measured. When using the terms "tobacco pH" or "product pH," the Agency and other laboratories that have conducted studies on smokeless tobacco pH are referring to the measured pH when the smokeless tobacco product is allowed to contact an aqueous environment such as water or saliva, as the product does when it is placed in the tobacco user's mouth. The studies on smokeless tobacco pH are designed to determine whether various brands of smokeless tobacco are designed, formulated, processed, or otherwise manipulated to control the pH of the product after contact with the aqueous environment in the user's mouth.

7. Smokeless tobacco industry comments cite two reports written by Jeffrey R. Idle criticizing smokeless tobacco pH studies and reports and FDA laboratory data. The comments also claim that Idle's analysis was sent to the Centers for Disease Control and Prevention (CDC) by the UST and was shared with "interested parties." The comments assume that CDC shared this analysis with FDA and question why the analysis is not in the

administrative record. Idle's analysis was not placed in the administrative record when the Jurisdictional Analysis was issued because the Agency was not aware of the document.

The Agency has reviewed the memorandum of Jeffrey Idle to UST entitled "FDA Proposed Rule: FDA Memoranda," dated December 13, 1995, and relevant portions of Idle's memorandum to UST dated February 9, 1995.[1082] For several reasons, some of which are described below, FDA concludes that Idle and the commenters either misunderstood or mischaracterized FDA's results and analyses. Moreover, Idle's review selects certain data favorable to his position, while ignoring data contrary to his position.

a. Idle's analysis asserts that FDA's reliance on the laboratory data showing graduated nicotine deliveries is not valid because the analytic methods used by the laboratories were not standardized.

FDA acknowledges that the four laboratories involved conducted independent analyses, using slightly different methods, to compare the nicotine deliveries of various brands of smokeless tobacco. Nonetheless, all four laboratories found a remarkably similar trend of graduated nicotine delivery across product lines. Contrary to Idle's comment, the fact that different laboratories, using different methods, reach the same conclusion increases—rather than diminishes—the reliability of the conclusion.

b. Idle's analysis asserts that the fact that a range of pH levels and free nicotine deliveries were observed for individual brands in the laboratory data shows that the manufacturers do not control pH or free nicotine. According to Idle's analysis, if pH levels

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[1082] Memorandum from Idle JR to U.S. Tobacco Company (Dec. 13, 1995). See AR (Vol. 529 Ref. 98, appendix 6).

Statement of Jeffrey R. Idle (Feb. 9, 1995). See AR (Vol. 526 Ref. 95, vol. VI).

and free nicotine delivery were controlled, the pH levels and free nicotine deliveries would never vary within a brand.

FDA disagrees with this comment. There are many explanations for the range of pH and free nicotine values observed within individual brands, including product fermentation during storage, natural variation in nicotine content and pH levels in tobacco leaves, and normal variation in laboratory analysis. Despite these variations, the data reveal a clear pattern of graduated pH levels and free nicotine delivery. It would have been surprising if no variations were measured by the laboratories.

c. Idle's analysis states that the majority of nicotine in all tobacco products is trapped inside the leaf particles and that acidic (low pH) conditions, not alkali (high pH) conditions, are necessary to leach nicotine out of smokeless tobacco. These assertions, however, are contradicted by the evidence in the administrative record. As discussed above, studies by FDA and other researchers, including researchers funded by the smokeless tobacco manufacturers, provide direct evidence that the release and absorption of nicotine increases as pH levels increase.

d. Idle's analysis states that the Skoal Long Cuts and Copenhagen are indistinguishable in terms of their nicotine content, rates of nicotine release, and pH levels. This assertion, however, is contradicted by the data measured in FDA laboratories. While the total nicotine content in Skoal Long Cuts and Copenhagen are similar, the products' pH and delivery of free nicotine differ substantially. For instance, FDA's data shows that Skoal Long Cut Cherry has a pH of 7.15 to 7.38 and a free nicotine delivery of 12.3% to 18.5%. These levels are substantially lower than Copenhagen, which has a pH of 7.71 to 8.14 and a free nicotine delivery of 32.7% to 56.5%. *See* section II.D.2.a., above.